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Reactivity of a 14-Membered Diacetal Dilactam Ring under Fast-Ion Bombardment and High-Energy Collisional Activation

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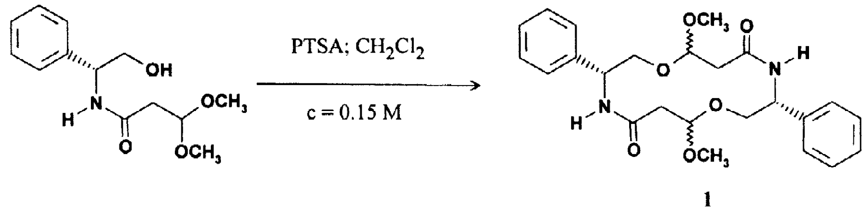
Abstract: The 14-membered diacetal dilactam ring **1** undergoes, at low pH and under fast-cesium ions bombardment, a substitution of its two acetal methoxy groups by a single molecule of glycerol (matrix) whereas near-neutral pH conditions lead only to protonation of the compound. The ability of compound **1** to complex alkali metal ions has been used for the comparison of the reactivities of its protonated and cationized forms under collisional activation. The unexpected loss of methane from the cationized methoxyls is the main fragmentation channel of the alkali metal complex ions. © 1998 Elsevier Science Ltd. All rights reserved.

The ionisation processes involving fast-particle bombardment (Liquid-Secondary Ion Mass Spectrometry, L-SIMS)[1] generate mainly, depending on the liquid matrix, protonated or "cationized" molecules due respectively to the attachment of proton or alkali metal ions to the compound of interest.

The conjugate effects of the particle bombardment on the sample solution and of the matrix (solvent) reactivity give rise to a rich and complex chemistry[2] including reduction-oxidation processes, acid-base reactions, substitution reactions, *etc.*[3] In particular, the matrix acidity has been shown to be responsible, in the case of glycerol acidified with HCl, for hemiketal hydroxy groups substitution by glyceryl moieties.[4] Further, the high-energy collision-induced dissociation (CID) spectra of various precursor ion types (protonated, cationized or substituted molecules) provide complementary information for both intrinsic chemical reactivity studies and structure elucidation of organic ions.

In this work, the potency of the combination of L-SIMS with high-energy tandem mass spectrometry (MS/MS) for reactivity and structure analysis purposes has been fully explored in the case of a macrocycle (**1**) which has been recently synthesised in our laboratory (Scheme 1).[5]



Scheme 1

Protonation and collision-induced dissociation of protonated molecules

The mass spectrum (L-SIMS) of compound **1**, recorded in glycerol,[6] displays a few ion peaks corresponding to the signals of the protonated molecule (*m/z* 443) and of two fragment ions at *m/z* 411 (loss of methanol from the protonated molecule) and *m/z* 222. The ionic signals, compared to those arising from the glycerol matrix, are weak.

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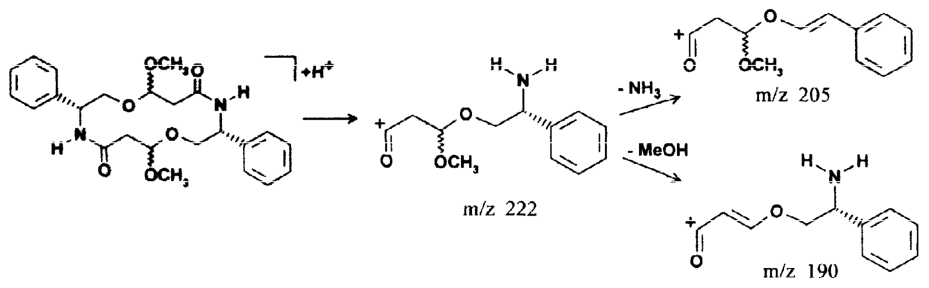


Scheme 2

The MS/MS spectrum of the $[M+H]^+$ precursor ions, devoid of the matrix ion peaks, confirms the fragmentation pathways observed. Further, under CID conditions,[7] the selected fragment ion at *m/z* 222 shows two main dissociation channels involving the loss of a methanol molecule (*m/z* 190) and the loss of ammonia (*m/z* 205). This result indicates that the "half-mass" peak at *m/z* 222 arises from the initial fragmentation of the two amide bonds of the protonated molecule rather than benzylic cleavages (Scheme 2).

Acidity effect and methoxyl substitution by glycerol in L-SIMS

The substitution, at low pH, of a hemiketal OH group by a glycerol molecule has been described in the case of indole alkaloids under fast-atom bombardment conditions.[4] Because of the diacetal structure of compound **1**, a similar reaction was expected to occur on both substitution sites leading to the condensation of two glycerol units with the macrocycle. In order to promote the substitution *in situ*, 1N HCl was added directly on the probe tip to the glycerol solution of the analyte. Under these conditions, the L-SIMS spectrum of compound **1** displayed, together with the ion peak corresponding to the protonated molecule at *m/z* 443, another signal at *m/z* 471 which was attributed to the substitution product $[M\text{-}2MeOH+Glycerol+H]^+$ in which the two methoxy groups were replaced by only one molecule of glycerol. The deuterated derivative **1**-d_6[8] led, under the same conditions, to an identical signal at *m/z* 471, thus demonstrating the loss of the labelled methoxyls and thereby confirming the occurrence of a substitution reaction by a glycerol molecule. In order to confirm the covalent structure of the glycerol adduct with compound **1**, the MS/MS spectrum of the ion at *m/z* 471 ($[2+H]^+$) was recorded. This spectrum (Figure 1), displaying various fragment ions, was in agreement with the bicyclic structure shown in Scheme 3. All attempts to reproduce this reaction in conventional solution phase mode were unsuccessful, thus suggesting a specific gas-phase process under L-SIMS conditions.

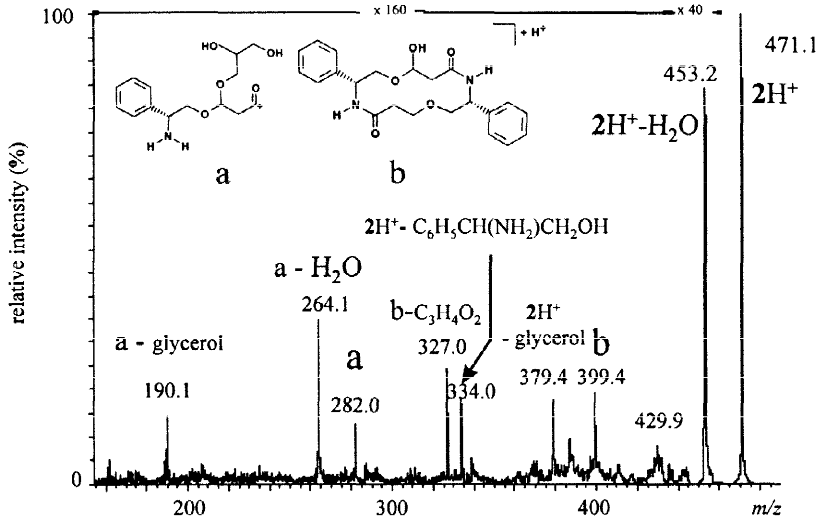
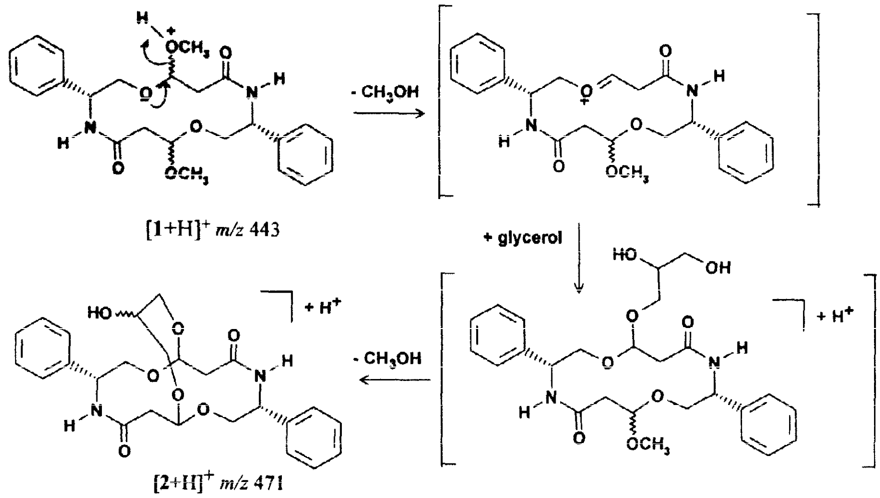


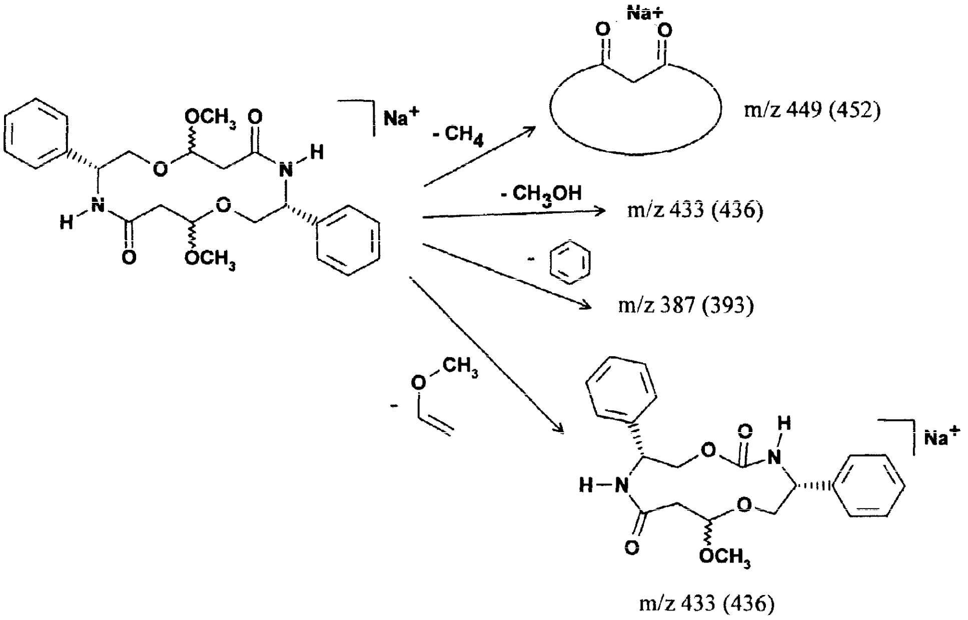
Figure 1. CID spectrum of the $[2+H]^+$ ion generated by L-SIMS from **1** (Matrix: glycerol + HCl)



Scheme 3

Collision-induced dissociation of cationized molecules $[M+C]^+$ (C = Li, Na, K)

The formation of cationized molecules $[M+C]^+$ by L-SIMS can be used for obtaining structural informations complementary to those provided by the MS/MS analysis of the protonated molecules. The MS/MS spectra of the cationized molecules reveal a markedly different behaviour, under collisional activation, than the protonated molecules. The loss of methanol from the methoxy groups which is the main fragmentation pathway of the $[M+H]^+$ ions becomes a minor process in the case of the $[M+C]^+$ ions. These ions fragment preferably by loss of a methane molecule, leading to a cationized diketonic compound (Scheme 4). This type of fragmentation was previously described in the case of methoxylated aromatic compounds which were cationized by transition metal ions (Cr^+), the loss of methane following a prior insertion of the metal ion in the $O-C(H_3)$ bond.[9] Such a mechanism cannot be suggested in the case of alkali metal ion complexes such as $[1+C]^+$ ions. Losses of other substituents (benzene, methanol), accompanied by different fragmentations of the macrocycle itself involving ring opening and/or ring contraction were also observed.



Scheme 4 (in brackets, fragments arising from the **1**-d_6 compound)

Examination of the hexadeuterated derivative **1-d_6** in which the two methoxyls were replaced by two OCD_3 groups and the comparison of the MS/MS spectra of the labelled and unlabelled $[M+Li]^+$, $[M+Na]^+$ and $[M+K]^+$ precursor ions allows the structural assignments for the main fragment ions, as shown in Scheme 4.

CONCLUSION

The ionisation process involving the fast-cesium ion bombardment of a glycerol solution of organic analyte generates various molecular species (protonated or cationized molecules in the positive mode) and can lead to chemical reactions in the liquid matrix. Collisional activation of the "sputtered" ions and analysis of the fragment ions by magnetic MS/MS show different behaviours of the different precursor ion types in their dissociation pathways.

Useful structural information can be deduced from these spectra, especially with the alkali metal cationized molecules.

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[#] On leave from URA CNRS 485, SEESIB, Université Blaise Pascal, Clermont-Ferrand, France.

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6. The L-SIMS spectra were obtained with a Zabspec-T five-sector tandem instrument (Micromass, Manchester, UK). The matrix was either glycerol or glycerol saturated with alkali iodides (LiI; NaI; KI). The primary cesium ions were accelerated at 30 keV and the secondary ion beam was introduced into the mass analyser at 8 keV kinetic energy. The mass scale *m/z* 1000-100 was scanned at 5 s/decade. The resolution was 1000 at 10 % valley.
7. For MS/MS experiments, the collision cell was set at 50 % of the accelerating voltage, thus allowing to a collision energy of 4 keV. The "metastable" fragment ions formed between the collision cell and the magnet were identified at 8 keV collision energy by coalescence of their signals with those of the fragments formed in the collision cell. The collision gas (helium) was used at a pressure leading to a 70 % attenuation of the precursor ion beam.
8. **1-d_6** was prepared from methyl-3,3-dimethoxy-d_6-propionate through the same reaction sequence of synthesis of **1**.[5]
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